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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,628	11/15/2001	David Botstein	P2730P1C30	7410

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EXAMINER	
WEGERT, SANDRA L	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/997,628	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	SANDRA WEGERT	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-123* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, and/or Claims

The appeal brief of 28 January 2008 has been received and considered. Upon further consideration, finality of the previous Office Action (mailed 30 March 2007) is *withdrawn* solely to clarify the issues for appeal, and to provide Applicant with an opportunity to respond accordingly.

35 U.S.C. §§ 101 and 112, First Paragraph - Utility

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 119-123 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility.

Claims 119-123 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

A portion of the basis for these rejections is withdrawn. Specifically, the examiner no longer asserts that **mRNA levels** are not predictive of polypeptide levels. Therefore, the

following references are no longer being relied upon to support the rejections: Chen et al., Hu et al., Haynes et al., Lian et al., Fessler et al., Nagaraja et al., Waghray et al., Sagnaliev et al., Lilley et al., Wildsmith et al., King et al., Celis et al., and Madoz-Gurpide et al. The following references cited and discussed by Applicants pertaining to the mRNA/polypeptide correlation issue will no longer be addressed: Futcher et al., Alberts and Lewin, Meric et al., Zhigang et al., Wang et al., Munaut et al. The basis of the maintained rejections is solely that **gene amplification levels** are not predictive of mRNA or polypeptide levels.

In the interest of clarity, the basis of the maintained rejections is set forth here:

The claims are directed to an antibody that binds specifically to the amino acid sequence of SEQ ID NO: 349. Claims are also presented to monoclonal, humanized, and labeled antibodies, and fragments that bind specifically. The specification discloses the polypeptide of SEQ ID NO: 349, also known as PRO1097. Applicants have gone on record as relying upon the gene amplification assay as providing utility and enablement for the claimed antibodies. See Appeal Brief (received 28 January 2008), p. 4, beginning of arguments.

At pages 539-555 of the specification, Example 170 discloses a gene amplification assay in which genomic DNA encoding PRO1097 had a ΔCt value of at least 1.0 for two out of 14 lung tumors and three out of 14 colon tumor samples when compared to a pooled control of blood DNA from several healthy volunteers. Example 170 asserts that gene amplification is associated with overexpression of the gene product (i.e., the polypeptide), indicating that the polypeptides are useful targets for therapeutic intervention in cancer and diagnostic determination of the presence of cancer (p. 539, lines 21-24). At page 548, ΔCt is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background

level of fluorescence. The specification further indicates that ΔCt is used as "a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results." It is noted that at page 548, it is stated that samples are used if their values are within 1 Ct of the 'normal standard'. It is further noted that the ΔCt values at pages 550-554 are expressed (a) with values to one one-hundredth of a unit (e.g. 1.29).

First, there are several problems with the data provided in this example. The art recognizes that lung and colon epithelium can be aneuploid without the presence of cancer. Specifically, Hittelman (2001, Ann. N. Y. Acad. Sci. 952:1-12, of record) reports that lung epithelium is at risk for cellular damage due to direct exposure to environmental pollutants and carcinogens, which result in aneuploidy **before** the epithelial cells turn cancerous. See especially p. 4, Figure 4. The gene amplification assay in the instant specification does not provide a comparison between the lung tumor samples and normal lung epithelium and does not correct for aneuploidy. Thus it is not clear that PRO1097 is amplified in cancerous lung epithelium more than in damaged (non-cancerous) lung epithelium. One skilled in the art would not conclude that PRO1097 is a diagnostic probe for lung cancer unless it is clear that PRO1097 is amplified to a clearly greater extent in true lung tumor tissue relative to non-cancerous lung epithelium. Regarding colon tissue, pre-malignant lesions and ulcerative colitis have been associated with aneuploidy. See Fleischhacker et al. (1995, Modern Pathology 8:360-365), especially p. 360, 1st paragraph of introduction. The gene amplification assay in the instant specification does not provide a comparison between the colon tumor samples and normal colon epithelium and does not correct for aneuploidy. Thus it is not clear that PRO1097 is amplified in cancerous colon

epithelium more than in damaged (non-cancerous) colon epithelium. One skilled in the art would not conclude that PRO1097 is a diagnostic probe for colon cancer unless it is clear that PRO1097 is amplified to a clearly greater extent in true colon tumor tissue relative to non-cancerous colon epithelium.

Second, even if the data had been corrected for aneuploidy and a proper control had been used, the data have no bearing on the utility of the claimed PRO1097 antibodies that bind to the disclosed polypeptide. The Utility of the claimed antibody depends on that of the disclosed PRO polypeptide, and in order for PRO1097 polypeptide to be overexpressed in tumors, amplified genomic DNA would have to correlate with increased mRNA levels and increased polypeptide levels. No data regarding PRO1097 mRNA or PRO1097 polypeptide levels in lung or colon tumors have been brought forth on the record. The art discloses that a correlation between genomic DNA levels and mRNA levels cannot be presumed, nor can any correlation between genomic DNA levels and polypeptide levels. A specific example of the lack of correlation between genomic DNA amplification and increased mRNA expression is provided by Pennica et al. (1998, PNAS USA 95:14717-14722, of record), who disclose that:

> "An analysis of *WISP*-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

See p. 14722, second paragraph of left column; pp. 14720-14721, "Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors." Another specific example is provided by Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that "Protein expression

is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template" (see abstract).

The *general* concept of gene amplification's lack of correlation with mRNA/protein overexpression in cancer tissue is addressed by Sen (2000, Curr. Opin. Oncol. 12:82-88). Specifically, Sen teaches that cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes. A slight amplification of a gene does not necessarily correlate with overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. Hittelman (2001, Ann. N. Y. Acad. Sci. 952:1-12) also speaks to this issue. Again, the data in the specification were not corrected for such aneuploidy events. Furthermore, Godbout et al. (1998, J. Biol. Chem. 273(33): 21161-8, of record) teach a general lack of correlation between gene amplification and mRNA/protein overexpression. The abstract of Godbout teaches "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. ***Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified***." (emphasis added). The protein encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state ***"It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell*** (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these

tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons." (emphasis added). There is no evidence in the instant application that PRO1097 confers any growth advantage to a cell, and thus it cannot be presumed that the protein is overexpressed because the genomic DNA including the gene being studied gene is amplified.

An additional reference that provides evidence that gene amplification does not generally lead to increased transcript is Li et al. (2006, Oncogene, Vol. 25, pages 2628-2635, of record). Li et al. used a functional approach that integrated simultaneous genomic and transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, right column, Li et al. state: "***In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels***, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but *lack biological relevance in terms of the development of lung adenocarcinoma*." Since more than half of the amplified genes were not overexpressed, Li et al. constitutes strong evidence that ***it is more likely than not that gene amplification does NOT correlate with increased protein levels***, absent evidence that the protein has biological relevance in cancer. There is no such evidence for PRO1097.

Therefore, data pertaining to PRO1097 genomic DNA do not indicate anything significant regarding the PRO1097 polypeptides or claimed cognate antibodies. The data do not support the specification's assertion that PRO1097 antibodies can be used as cancer diagnostic agents. Significant further research would have been required of the skilled artisan to reasonably confirm that the disclosed PRO1097 polypeptides are overexpressed in any cancer to the extent that they could be used as cancer diagnostic agents; thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO1097 polypeptide levels are also different between specific cancerous and normal tissues (such that detection with the claimed antibodies would be a useful function), the proposed use of the PRO1097 **antibodies** as diagnostic markers and the PRO1097 **polypeptides** as therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

In view of the preponderance of evidence supporting the rejections (Pennica et al., Konopka et al., Fleischhacker et al., Sen, Hittelman, Godbout et al., and Li et al., all of which are of record and have been previously discussed), the rejections are properly maintained.

Applicant's arguments pertaining to the remaining issues (Appeal Brief, 28 January 2008) have been fully considered but are not found to be persuasive for the following reasons.

Applicants' detailed arguments begin at p. 7 of the appeal brief. Applicants begin with a review of the legal standard for utility, with which the examiner takes no issue.

Beginning at pp. 10-11 of the brief, Applicants review Example 170, and refer to the Goddard declaration as establishing that an amplification of at least 2-fold is significant and indicative of a cancer diagnostic marker. The Goddard declaration under 37 CFR 1.132 filed 22 August 2005 is insufficient to overcome the rejection of claims 119-123 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action for the following reasons. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not a 2.313 fold to 2.346 fold amplification in two lung tumors and a 2.114 fold to 2.532 fold amplification in three out of fourteen colon tumors is significant, and whether such data have any relevance to the claimed subject matter, i.e., PRO1097 polypeptides and variants thereof. The significance can be questioned based on the strength of opposing evidence. In the instant case, the control used was not a matched non-tumor colon sample but rather was a pooled DNA sample from blood of healthy subjects. The art uses matched tissue samples (see Pennica et al., Konopka et al.). This art, as well as the Fleischhacker et al., Sen, Hittelman, Godbout et al., and Li et al. references cited above, constitute strong opposing evidence as to whether or not the

claimed polypeptides and variants thereof have utility and enablement based on a presumption of overexpression in view of gene amplification data. Finally, while the Goddard declaration speaks to the utility and enablement of genes, it does not speak to whether or not the encoded proteins or variants thereof are also found at increased levels in cancerous tissues. Since the claims under examination are directed to polypeptides, not genes, this question is critical. Applicant urges that it is more likely than not that an increase in genomic DNA copy number correlates with an increase in protein levels. At p. 13, Applicant criticizes Pennica et al. and Konopka et al. as not being specific to PRO1097, instead as being specific to other genes, and not establishing a general trend. This has been fully considered but is not found to be persuasive. The instant application also presents data from a single gene at a time and makes conclusions about gene products from genomic DNA data. Pennica and Konopka constitute evidence that it cannot be assumed that amplified genomic DNA results in overexpressed gene product. Godbout et al. and Li et al. also provide evidence to this effect. Finally, Fleischhacker et al., Sen, and Hittelman constitute evidence that, in general, non-cancerous epithelial tissues are frequently aneuploid, and thus an increase in genomic DNA is not diagnostic of cancer. Beginning at p. 17, Applicant discuses the Godbout et al. and Bea et al. references. Applicant argues that Bea et al. supports Applicant's position that gene amplification is correlated with both increased mRNA and protein expression. Applicant argues that the examiner's concerns regarding Godbout et al. (specifically, that Godbout et al. does structure/function analysis while the specification does not) are not relevant, since the instant specification does not assert that PRO1097 is similar to Godbout et al.'s DDX1 gene. Applicant urges that a structure/function analysis is not required for utility. This has been fully considered but is not found to be

persuasive. Contrary to Applicant's characterization, Godbout et al. is relied upon for teaching that, "***Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified***." (emphasis added). The protein encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state ***"It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell*** (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons." (emphasis added). There is no evidence in the instant application that PRO1097 confers any growth advantage to a cell, and thus it cannot be presumed that the protein is overexpressed because the genomic DNA including the gene being studied gene is amplified. Regarding Bea et al., it is not unexpected that a putative oncogene that seems to participate in cell cycle regulation and senescence, when amplified in the genome, would also be amplified as mRNA and have correspondingly increased protein expression. PRO1097 is not a putative oncogene, and the function of the encoded protein

is not known. Godbout et al. and Bea et al. clearly point out that whether or not a protein is over-expressed depends strictly upon the function of the protein. The instant specification has not established that over-expression of PRO1097 provides a growth advantage to a cell, and thus it cannot be said that Bea et al. and Godbout et al. constitute evidence to support Applicant's position. In fact, Godbout et al. and Bea et al. support the instant rejection.

At p. 24, Applicant discusses the Li et al. reference. Applicant urges that Li et al. acknowledge that their results differed from those of Hyman et al. and Pollack et al., and note that the difference may be due to different methodologies. Applicant refers to the supplemental information accompanying the Li et al. article, enclosed as Exhibit A. Applicant urges that Li et al. used an amplification copy ratio of only 1.4, which is not significant according to the Goddard declaration, and that a copy number of at least 2 was necessary. This has been fully considered but is not found to be persuasive. First, it is noted that Hyman et al. also found that less than half of the amplified genes were overexpressed at the mRNA level, even though they only investigated genes in genomic DNA regions that were amplified at least 2-fold (argued in more detail above). Furthermore, Li et al. did not limit their studies to genes that were amplified at less than 2-fold. In fact, the supplemental information indicates that some of the samples were required to bind with a probe requiring at least 2-fold amplification:

"Genes with copy number ratio > 1.40 (representing the upper 5% of the CGH ratios across all experiments) were considered to be overrepresented. A genomic fragment that contained six or more adjacent probes showing a copy number ratio > 1.40, or a region with at least three adjacent probes with a copy number ratio > 1.40 **and no less than one probe with a ratio > 2.0**, were considered to be amplicons." (emphasis added, from 1st page of supplemental material)

At p. 25, Applicant argues that Hittelman supports Applicant's position. Specifically, Applicant urges that Hittelman support that there is utility for an aneuploidy gene at least as a marker for cancer or precancerous cells or damaged tissue, and thus such a gene is useful as a marker for

cancer or risk of cancer. This has been fully considered but is not found to be persuasive. First, while the argument is pertinent with regard to PRO1097 genes, it does not address the claimed subject matter, which is PRO1097 antibodies that bind to the PRO polypeptide. It is important to clarify that no evidence has been brought forward to establish that the PRO1097 **polypeptide** is amplified in any lung or colon tumors. Since the PRO1097 polypeptide is not amplified in lung or colon tumors, there is no reason to detect it with the claimed antibody. Furthermore, nowhere does the specification assert a utility for the disclosed PRO1097 polypeptides or claimed antibodies as being useful to diagnose subjects *at risk for* developing lung or colon cancer, and therefore this argument also is not persuasive. While it might be argued in hindsight that PRO1097 would still be a marker at least for precancerous, or damaged, colon epithelium, such is not suggested by the specification as originally filed. Finally, even if it could be established that the PRO1097 gene is significantly amplified in colon carcinomas compared to healthy colon tissue, it does not follow that PRO1097 polypeptide and variants thereof would also be over-expressed. One skilled in the art would expect that such variant sequences would not reasonably be expected to show changed levels for a particular disease state.

Beginning at p. 20, Applicant acknowledges that, in certain instances, DNA/mRNA and protein levels do not correlate. Applicant argues, however, that increased gene and transcript levels mostly correlate with increased protein levels, even if accurate predictions of proteins could not be made. Applicant again argues that the gene amplification data establish a credible, specific, and substantial patentable utility for the PRO1097 polypeptide. Applicant points to the assertion in the specification that gene amplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for of the claimed antibodies for

therapeutic intervention and diagnostic determination of certain cancers. Applicant argues that ample evidence has been submitted to show that, in general, if a gene is amplified in cancer, then it is more likely than not that the encoded protein is also overexpressed. Specifically, Applicant refers to the Polakis declaration of 5 July 2006. This has been fully considered but is not found to be persuasive. The preponderance of the evidence establishes that it is more likely than not that gene amplification does not correlate with increased protein expression. See Pennica et al., Konopka et al., Sen, Hittelman, Godbout et al., Li et al., and Hanna and Mornin. The Polakis declaration under 37 CFR 1.132 filed 5 July 2006 is insufficient to overcome the rejection of claims 119-123 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action because the declaration focuses on the question of whether or not mRNA levels are predictive of protein levels. As explained above, the examiner is no longer arguing this point. Since the Polakis declaration does not address the question of whether or not amplified genomic DNA is predictive of increased polypeptide levels, they are no longer considered pertinent to the rejection.

At p. 23, Applicant concludes that, based on the asserted utility for PRO1097 in the diagnosis of selected lung and colon tumors, the reduction to practice of the PRO1097 protein sequence, the disclosure of methods for making polypeptides and chimeric polypeptides comprising PRO1097 and the claimed antibodies that bind PRO1097, and example 170 regarding the gene amplification assay, one skilled in the art would know exactly how to make and use the claimed antibodies for diagnosis of lung and colon cancer without undue experimentation. Applicant concludes that the utility of the claimed PRO1097 antibodies has been achieved. This has been fully considered but is not found to be persuasive for the following

reasons. Regarding the gene amplification assay itself, it is noted that the assay did not correct for aneuploidy, which is a common feature of non-cancerous, damaged colon epithelium (evidenced by Fleischhacker et al.). Evidence has also been brought forth that aneuploidy is characteristic of other damaged epithelial tissues (Sen, Hittelman). Gene amplification publications used matched tissue controls, unlike applicant (Pennica et al., Konopka et al., Godbout et al., Li et al.). Contrary to Applicant's assertion, the state of the art indicates that gene amplification is not generally associated with overexpression of the encoded gene product, as evidenced by Sen, Pennica et al., Konopka et al., Godbout et al., Hyman et al., and Li et al. Since significant further research would have been required of the skilled artisan to reasonably confirm that the disclosed PRO1097 polypeptides are overexpressed in any cancer to the extent that there detection by the claimed antibody would be useful as a cancer diagnostic agent, the asserted utility is not substantial. In the absence of information regarding whether or not PRO1097 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO1097 **antibodies** as diagnostic markers and therapeutic products are simply starting points for further research and investigation into potential practical uses of the polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to

engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Hanna and Mornin (1999, Pathology Associates Medical Laboratories, of record) also supports the instant rejections. Hanna and Mornin provide another important example of a lack of correlation between gene amplification and mRNA/protein overexpression, wherein diagnosis of breast cancer included testing both the amplification of the HER-2/neu gene as well as over-expression of the HER-2/neu gene product. Thus Hanna and Mornin provide evidence that the level of protein expression must be tested empirically to determine whether or not the antibody can be used as a diagnostic marker for a cancer. The specification does not provide data as to whether or not the protein level of PRO1097 was tested in normal and cancerous tissue, and thus the skilled artisan *must* perform additional experiments, as directed by the art. Since the asserted utility for the claimed antibodies is not in currently available form, and further experimentation is *required* to reasonably confirm the asserted real-world use, the asserted utility is not substantial.

Conclusion

No claims are allowed.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be

reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Manjunath Rao, can be reached at (571) **272-0939**.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

/SLW/
24 April 2008

/Manjunath N. Rao, /
Supervisory Patent Examiner, Art Unit 1647